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# Mechanisms underlying the effects of nutrition, adiposity and physical activity on colorectal cancer risk

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## Abstract

Lifestyle factors including diet, body fatness and physical activity modulate the risk of developing colorectal cancer (CRC) and it is estimated that over half of CRC cases in the UK are linked to such factors. This review focuses on describing the underlying mechanisms behind the effects of lifestyle factors (predominantly dietary) for which there is strong (convincing or probable) evidence for effects on CRC risk, described in the recently published World Cancer Research Fund/American Institute for Cancer Research colorectal cancer report. These include a protective effect of physical activity, wholegrains and dietary fibre, dairy products and calcium supplements, and increased risk associated with red and processed meats, alcoholic drinks and higher body fatness. The postulated mechanisms underlying the effects of lifestyle on CRC risk, including effects on inflammation, insulin resistance and the microbiome, and affecting pathways involved in the regulation of cell proliferation, differentiation, DNA repair and apoptosis are described. Epigenetic mechanisms that are dysregulated in colorectal carcinogenesis leading to aberrant patterns of DNA methylation and aberrant expression of microRNAs may also be modulated by lifestyle factors and consequently modulate CRC risk. It is likely that an interplay of these mechanisms is involved in the modulation of CRC risk as well as a combination of these lifestyle factors.

**Keywords:** adiposity, colorectal cancer, diet, mechanisms, nutrition, physical activity

## Introduction

Colorectal cancer (CRC) risk is strongly modulated by lifestyle factors including diet, physical activity and body fatness. It has been estimated that 54% of CRC cases in the UK are linked with such factors, suggesting that a large proportion of cases may be prevented by adopting a healthier lifestyle (Brown *et al.* 2018). The recently published World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) report has reviewed the literature (mainly epidemiological studies) for evidence for the links between diet, nutrition, physical activity and cancer, including CRC (WCRF/AICR 2018). The potential mechanisms underlying the effects of diet-related factors, for which WCRF/AICR consider there is strong evidence (subdivided into 'convincing' or 'probable' evidence) for an effect on CRC risk (Table 1), will be the focus of this review. The

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WCRF/AICR report concluded that for CRC there is convincing evidence for a protective effect of physical activity, and an increased risk with high intakes of processed meat and alcohol as well as with increased body fatness and adult attained height (not discussed in this review). The evidence that higher intakes of wholegrains, dietary fibre, dairy products and calcium supplements are protective was described by WCRF/AICR as probable.

The mechanisms underlying the effects of lifestyle factors, including nutrition, on CRC risk are not fully understood and are likely to include overlapping mechanisms. As chronic inflammation causes genomic damage and drives colorectal carcinogenesis, those factors that induce inflammation, such as obesity and consumption of certain nutrients, are likely to exacerbate CRC risk. This risk may also be modulated via effects on insulin sensitivity and associated hormones and growth factors, such as adiponectin and insulin-like growth factor 1 (IGF-1). More recently, it has been discovered that the epigenome is modulated by dietary factors including non-nutrient bioactives (Mathers *et al.* 2010). The epigenome is a consortium of chemical marks (DNA methylation and post-translational modification of histones) and molecules (*e.g.* non-coding RNAs) that regulate gene expression without changes in the gene sequence. In cancers and other diseases, there are multiple changes in the epigenome, many of which are causal in the pathogenesis of the disease. Therefore, altered epigenetic mechanisms play a role in modulation of CRC risk and this may be an important mechanism of action of dietary factors. For example, butyrate [a short-chain fatty acid (SCFA) product of dietary fibre fermentation] is a well-established modulator of histone acetylation and has been shown to modulate the expression of microRNAs (miRNAs). The microbiome is also a key player in the regulation of health and diseases, particularly those in the gut such as inflammatory bowel disease (IBD) and CRC. The abundance of individual bacterial and fungal species and the diversity of the gut microbiota are influenced by lifestyle factors, such as obesity and the intake of dietary fibre and fatty acids, which may also modulate CRC risk (Maruvada *et al.* 2017; Makki *et al.* 2018).

**Table 1** Strong evidence (convincing or probable) for effects of diet, nutrition and physical activity on colorectal cancer risk. Adapted from the WCRF/AICR report (WCRF/AICR 2018)

| | | Decreases risk | Increases risk |
|---|---|---|---|
| Strong evidence | Convincing | Physical activity | Processed meat<br>Alcoholic drinks<br>Body fatness |
| | Probable | Wholegrains<br>Foods containing dietary fibre<br>Dairy products<br>Calcium supplements | Red meat |

## Physical activity

The WCRF/AICR panel concluded that there is convincing evidence for lower CRC risk with increased physical activity (WCRF/AICR 2018). Physical activity is one of the strongest chemoprotective lifestyle factors against CRC and observational studies estimate that 14% of CRC cases are attributable to physical inactivity (Colditz *et al.* 1997; Samad *et al.* 2005). However, there have been no physical activity intervention studies with CRC as the outcome, and most of the evidence is from observational studies. In the context of secondary prevention, a systematic review and meta-analysis of five randomised controlled trials in CRC patients concluded that there was insufficient robust evidence to make recommendations on physical activity in this group (Cramer *et al.* 2014). In a mouse model of intestinal tumorigenesis, an exercise intervention comprising running for 1 hour per day for 6 days per week at a speed of 15 miles per minute (between the ages of 4 and 16 weeks) was associated with a significantly reduced number of large polyps compared with sedentary mice (McClellan *et al.* 2014). In a similar mouse model of CRC, treadmill running for up to 12 weeks (30–60 minutes per day, 5 days per week) significantly reduced the number of large intestinal adenomas and appeared to reduce tumour multiplicity (Basterfield & Mathers 2010). The authors concluded that the effects of exercise on intestinal tumorigenesis may have been mediated by colonic butyrate levels; whereby the exercised mice had significantly greater levels of butyrate in colonic digesta and there was a trend for an inverse relationship between butyrate molar proportion and the total number of adenomas.

Physical activity may indirectly modulate CRC risk via its beneficial effects on body fatness (discussed in the following section on body fatness), and consequently on insulin resistance and inflammation. Directly, physical activity stimulates digestion and reduces food transit time and therefore may reduce the exposure of the large bowel to potential carcinogens (Peters *et al.* 2001). Physical activity may also

help to normalise markers that are dysregulated in CRC. For example, circulating concentrations of insulin, leptin and growth factors (discussed in the following section on body fatness) improve with exercise (Winzer *et al.* 2011).

Increased concentrations of bile acids in faeces and serum have been associated with several cancers, including CRC and other gastrointestinal cancers (Bayerdorffer *et al.* 1995; Ajouz *et al.* 2014), and significantly increased faecal bile acids have been observed in CRC patients (Imray *et al.* 1992). Secondary bile acids are the products of bile acid fermentation by the gut microbiota and associated with detrimental effects on the colorectal mucosa including oxidative DNA damage, reduced DNA repair and stimulation of cell proliferation and inflammation (Ajouz *et al.* 2014; Dossa *et al.* 2016). The secondary bile acids, deoxycholic acid and lithocholic acid, and cholate promote the production of reactive oxygen species (ROS), which induce DNA damage and subsequently genomic instability, which is a hallmark of cancer (Hanahan & Weinberg 2011; Ajouz *et al.* 2014). In humans, the evidence for the effects of physical activity on bile acid levels is limited. In a cross-sectional study of 735 colorectal adenoma patients, participants in the highest quartile of recreational physical activity duration had significantly lower faecal bile acid concentrations than those in the lowest quartile after adjusting for factors such as age, dietary fibre intake and BMI (Wertheim *et al.* 2009). Male distance runners have lower faecal bile acid concentrations than sedentary individuals but this difference disappeared following adjustment for dietary fibre intake whereby runners had a greater consumption of dietary fibre (Sutherland *et al.* 1991). In 30 healthy individuals, running reduced serum concentration of total bile acids by almost 50% (Danese *et al.* 2017). These effects may result from acute reduction in serum cholesterol, which subsequently limits bile acid synthesis in the liver, and by the modulation of triglyceride and/or cholesterol levels. In individuals with low triglyceride concentrations, higher physical activity reduced faecal bile acids by almost 40% (Wertheim *et al.* 2009).

Prostaglandin levels in the colonic mucosa have been associated with CRC and other cancers (Wang & Dubois 2006; Wang & DuBois 2013). A study in 63 participants at higher risk of CRC (with a history of polyps) quantified prostaglandin E2 levels in the rectal mucosa and observed that leisure time physical activity (assessed through a self-completed questionnaire) was inversely correlated with prostaglandin E2 concentrations (Martinez *et al.* 1999). A fivefold increase in activity levels was associated with almost a third reduction in prostaglandin E2, suggesting that this could be another potential mechanism for the effects of physical activity on CRC risk.

In humans, physical activity has been associated with multiple beneficial effects on the immune system including a reduction in senescent T cells, reduced inflammatory responses and inflammatory cytokine levels and increased natural killer cell activity (Shephard *et al.* 1994). However, the effects on the immune system may vary depending on the type, intensity and duration of the physical activity (Kruger *et al.* 2016). In a mouse model of intestinal tumorigenesis already described, an exercise intervention resulted in a reduction in macrophages and regulatory T cells and an increase in markers of cytotoxic T cells, and this was associated with a reduced number of large polyps compared with sedentary mice (McClellan *et al.* 2014). In a human study, physical exercise may significantly improve anti-cancer immune function in cancer survivors (Fairey *et al.* 2002).

The effects of physical activity on CRC risk may be mediated via effects on cell proliferation and apoptosis in the large bowel. In sedentary individuals, a 12-month intervention of 60-minute moderate-to-vigorous aerobic exercise 6 days per week resulted in a significant reduction in markers of colonic crypt cell proliferation, such as the proportion of proliferating cells in the upper half of the crypt, in male participants exercising for a minimum of 250 minutes per week (McTiernan *et al.* 2006). A trend was also observed for a greater reduction in cell proliferation with increasing amounts of exercise. In the same study, assessment of apoptotic markers revealed a significant reduction in the pro-apoptotic protein Bax in the base of the crypts in males, and middle and top of the crypts in females randomised to the exercise arm (Campbell *et al.* 2007).

More recently, the impact of physical activity on the gut microbiome, and consequently the modulation of gut health via effects on, for example, inflammation, has been investigated. The microbiome plays a key role in maintenance of the healthy mucosa and adequate gastrointestinal immune function. Disturbances in the microbiome may lead to inadequate immune function and dysbiosis is observed in diseases such as inflammatory bowel disease (IBD), CRC (Tilg *et al.* 2018) and non-gastrointestinal diseases, such as allergies and asthma (Fujimura & Lynch 2015; Huang & Boushey 2015). In IBDs, such as ulcerative colitis, exercise has been shown to improve gastrointestinal

immune function and the microbiota–immune system; however, most of the evidence comes from animal studies and human data are limited (Cook *et al.* 2016).

Oxidative stress and the generation of ROS and free radicals may promote colorectal carcinogenesis. The high cell turnover and metabolic rate of colorectal epithelial cells make them particularly vulnerable to damage by ROS and oxidative stress. DNA damage in these cells, particularly proliferating cells, can result in replicative errors and genomic instability and mutagenesis (Saha *et al.* 2017). Improvements in antioxidant capacity with physical activity via effects on signalling pathways such as MAPK and NFKB, which have been shown to be activated with exercise in both humans and animal models, result in protection of cells against free radicals and ROS (Perse 2013).

### Body fatness

Obesity is a well-established risk factor for CRC and a systematic review of prospective studies, including approximately 9 million participants, reported a 33% increase in CRC risk in obese individuals compared with those with a normal BMI (Ma *et al.* 2013). Furthermore, individuals with a large waist circumference had a 46% increased risk of CRC (Ma *et al.* 2013). In a meta-analysis including over 50 000 CRC cases, the increases in CRC risk associated with weight, BMI and waist circumference (a marker of central adiposity) were 2% (per 5 kg increase in weight), 6% (per 5 kg/m$^2$ increase in BMI) and 2% (per 10 cm increase in waist circumference), respectively (Abar *et al.* 2018). A meta-analysis of 30 prospective studies concluded that the effects of obesity on CRC risk are dependent on sex and cancer site (Larsson & Wolk 2007). In both males and females, increased waist circumference and waist–hip ratio were associated with a significant increase in colon cancer risk. Thirty percent and 12% increased risk of colon cancer was observed with a 5-unit increase in BMI in males and females, respectively; however, an effect of BMI on rectal cancer risk was observed only in males.

Obesity is associated with chronic low-grade systemic inflammation, which is perhaps the primary mechanism associated with increasing CRC risk. CRC is an inflammatory disorder and chronic inflammation, such as that observed in patients with IBD, is associated with increased CRC risk (Kim & Chang 2014). This risk rises with disease duration: CRC risk may be increased by almost 20% in patients with >30 years of inflammatory disorders (Eaden *et al.* 2001). The chronic low-grade inflammation induced by obesity, evidenced, for example, by increased expression of inflammatory markers such as C-reactive protein (CRP) and interleukins (*e.g.* IL-6), is therefore likely to be a key mechanism (Ellulu *et al.* 2017). Raised CRP concentrations have been associated with CRC risk and incidence (Mazhar & Ngan 2006). With increased adiposity, there is an increase in pro-inflammatory molecules secreted from adipocytes and macrophages that reside in white adipose tissue. Tumour necrosis factor-α (TNF-α) is a pro-inflammatory cytokine that is constitutively expressed by adipocytes and therefore contributes to the stimulation of an inflammatory state associated with obesity, and this correlates positively with BMI (Hotamisligil *et al.* 1993). Inflammation may also exacerbate the obesity-induced insulin resistance; for example, the inflammatory cytokines (*e.g.* IL-6) may disrupt insulin signalling (Shoelson *et al.* 2006).

Another potential mechanism relates to the effects of insulin resistance and regulating hormones such as insulin and adipokines. Insulin resistance describes the inability of cells to respond to insulin concentrations, resulting in increased blood levels of insulin (hyperinsulinaemia) being required to regulate glucose concentrations (Gunter & Leitzmann 2006). Insulin resistance results from an increase in blood levels of free fatty acids, resistin and TNF-α, and a reduction in adiponectin release by adipose tissue (illustrated in Fig. 1). There is an overlap between risk factors for the development of insulin resistance and for CRC, such as surplus energy intake, physical inactivity, a low-fibre diet (Weickert & Pfeiffer 2018) and body fatness, providing a plausible mechanism underlying the effects of such lifestyle and dietary factors on the risk of developing CRC. Chronically elevated insulin levels (hyperinsulinaemia) have been associated with cancers, including CRC and breast cancer. Furthermore, patients with other diseases associated with insulin resistance, such as metabolic syndrome and type 2 diabetes mellitus, have a raised risk of developing CRC (Stocks *et al.* 2011; Deng *et al.* 2012). Insulin resistance is associated with increased levels of insulin, glucose, triglycerides and non-esterified fatty acids. The resulting hyperinsulinaemia has been associated with induced colonic epithelial cell growth and inhibited apoptosis, which animal and human studies suggest may promote tumour development (Keku *et al.* 2005; Tran *et al.* 2006).

The effects of insulin may result directly, or may be consequences of, the effects on hormones such IGF-1 and sex hormones such as estrogens (Calle & Kaaks

 

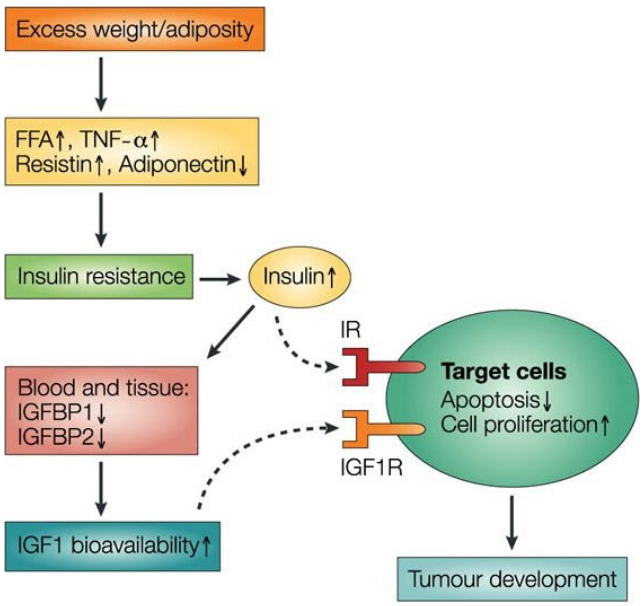


**Figure 1** Obesity-induced insulin resistance and the promotion of tumour development. Reproduced with permission (Calle & Kaaks 2004). FFA, free fatty acids; IGF-1, insulin-like growth factor-1; IGFBP1, insulin-like growth factor-binding protein 1; IGFBP2, insulin-like growth factor-binding protein 2; IGF1R, insulin-like growth factor-1 receptor; IR, insulin receptor; TNF-α, tumour necrosis factor-α. [Colour figure can be viewed at wileyonlinelibrary.com]

2004). It is likely that these mechanisms are simultaneously in play to varying extents. It is the induction of cell proliferation and inhibition of apoptosis in colorectal mucosal cells that may be the predominant mechanism behind the effects of the altered levels of these circulating factors, an excess of which promotes tumorigenesis in colonocytes and leads to dysregulation of signalling pathways, such as the MAPK pathway. In addition, peroxisome proliferator-activated receptors (PPARs) that are present in the colorectum may be impaired by these molecules, such as triglycerides, consequently altering the regulation of processes such as inflammation, homeostasis, differentiation, proliferation and apoptosis (Yehuda-Shnaidman & Schwartz 2012). There is evidence for protective effects of PPAR-gamma in inhibiting proliferation of colorectal tumours in mice, and reduced PPAR-alpha expression and protein levels have been reported in human neoplastic, compared with non-malignant human colorectal mucosa (Jackson *et al.* 2003).

Furthermore, an increase in glucose and fatty acids leads to metabolic dysregulation, oxidative stress and effects in pathways implicated in carcinogenesis, which together may promote carcinogenesis (Gunter & Leitzmann 2006). The production of ROS and DNA damage coupled with a reduction in antioxidants resulting from adiposity and hyperglycaemia and the associated surplus energy is another mechanism for the effects of obesity on colorectal carcinogenesis (Gunter & Leitzmann 2006).

In obese individuals, the levels and bioactivity of free insulin-like growth factor 1 (IGF-1) are increased (Frystyk *et al.* 1995; Nam *et al.* 1997). IGF-1 concentrations have been associated with increased risk of CRC as well as adenomas, precursors to CRC, which may result from the anti-apoptotic effects of IGF-1 (Vigneri *et al.* 2015). Insulin and IGF levels, coupled with a reduction in IGF-binding protein (IGFBP), that are raised with insulin resistance, promote cellular proliferation and differentiation (Giovannucci 2001). The majority of the evidence for this comes from studies in patients with acromegaly, a hormonal disorder associated with excess production and secretion of growth hormone by the pituitary gland, who have increased epithelial cell proliferation (Cats *et al.* 1996) and a greater CRC incidence (Jenkins *et al.* 2002; Renehan *et al.* 2003).

Leptin and adiponectin, two adipocytokines secreted by adipose tissue, are implicated in colorectal carcinogenesis. BMI is inversely correlated with circulating levels of adiponectin, an insulin-sensitising hormone that regulates intracellular signalling pathways such as adenosine monophosphate-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) (Sugiyama *et al.* 2009). In a case–control study, plasma adiponectin was inversely correlated with CRC risk in men, and participants in the highest quintile had a 60% lower CRC risk compared with those in the lowest quintile (Wei *et al.* 2005). On the other hand, leptin concentrations increase with increasing BMI and body fatness (Sauter *et al.* 2004; Ruhl *et al.* 2007; Paul *et al.* 2011), and it is overexpressed in CRC and implicated in cancer initiation and progression (Koda *et al.* 2007). The effects of adiponectin and leptin on CRC risk may result from the inhibition of apoptosis and the promotion of cell proliferation (Aparicio *et al.* 2005; Ogunwobi & Beales 2007; Fenton & Birmingham 2010; Nigro *et al.* 2018). Adiponectin and leptin may also modulate CRC risk via effects on inflammation (Sitaraman *et al.* 2004; Ouchi & Walsh 2007; Drew 2012); for example, adiponectin has been shown to modulate the expression of genes involved in chronic inflammation and tumorigenesis (Saxena *et al.* 2012).

Adiposity and obesity may also affect levels of steroid hormones, such as androgens and estrogens, which

may consequently modulate CRC risk. BMI correlates positively with the estrogens estrone and estradiol (Schairer *et al.* 2016). Increased sex hormones may also result from obesity-induced insulin resistance, whereby sex hormone-binding globulin (a glycoprotein that binds androgen and estrogen) synthesis is inhibited by and is inversely correlated with IGF-1 (Pasquali *et al.* 1995; Daka *et al.* 2013). Increased bioavailability of testosterone and estradiol in females may also result from a reduction in sex hormone-binding globulin, which in turn is a consequence of adiposity and increased circulating insulin and IGF-1.

The microbiota profile of obese individuals is different compared with healthy individuals, including an increase in bacteria such as the *Firmicutes* species and a reduction in *Bacteroidetes* (Wolf & Lorenz 2012). Recent research suggests that the gut microbiome is associated with wide effects on health and disease, including gastrointestinal health and the risk of diseases such as IBD and CRC (Tilg *et al.* 2018; Valdes *et al.* 2018). Levels and altered diversity of the gut microbiota (dysbiosis) may be modulated by dietary factors, such as dietary fibre intake (discussed in the following section on wholegrains and dietary fibre), and consequently may have health-promoting effects, such as an increase in SCFA production, reduction in gut inflammation, improved insulin sensitivity and increased antioxidant production. Obesity itself is associated with a change in microbiota composition (Turnbaugh *et al.* 2009) [*e.g.* a greater ratio of Firmicutes to Bacteroidetes (Ley *et al.* 2006)], which, in turn, may promote diet-induced obesity. The potential effects of microbiota dysbiosis on obesity and disease risk have been suggested to result from mechanisms such as the dysregulation of gut hormones, inflammation and abnormal energy regulation (Valdes *et al.* 2018). Due to the key role of inflammation in colorectal carcinogenesis, the promotion of low-grade inflammation by microbiota dysbiosis is an important mechanism for the effects on CRC risk. It is likely to be the simultaneous effects of the gut microbiome itself and its metabolic products which collectively influence CRC risk (Louis *et al.* 2014).

## Wholegrains and dietary fibre

Dietary fibre is found in wholegrains, which include germ, endosperm and bran as well as vitamins, minerals and phytochemicals, and other foods such as fruit, vegetables and pulses (Jacobs *et al.* 1998). The observation of a probable chemoprotective effect of dietary fibre on CRC was originally proposed in the 1970s by Dr. Burkitt who observed low CRC rates in Western Africans whose habitual diet was very high in dietary fibre (Burkitt 1971). A more recent systematic review and meta-analysis of 25 prospective studies found inverse associations between intakes of dietary fibre and wholegrains, and CRC risk (Aune *et al.* 2011). In a meta-analysis of 20 studies including over 10 000 colorectal adenoma patients, a 28% reduction in the risk of adenomas was associated with a daily 10 g increase in intake of dietary fibre (Ben *et al.* 2014). In the *European Prospective Investigation into Cancer* (*EPIC*) study, an inverse relationship between dietary fibre intake and CRC incidence was observed, leading the authors to conclude that doubling dietary fibre intake could reduce the number of CRC cases by 40% (Bingham *et al.* 2003). Higher total intake of wholegrains, found in foods such as wholegrain breads, oatmeal, breakfast cereals and brown rice, was associated with an 18% reduction in risk of colon but not rectal cancer, and per daily increment of three servings, CRC risk was reduced by 17% (Aune *et al.* 2011).

For some time, it has been suggested that both wholegrains and dietary fibre may reduce CRC cancer risk by reducing exposure of the lining of the large bowel to carcinogens by increasing faecal bulk, and consequently diluting carcinogens and reducing transit time (Burkitt *et al.* 1972; Lipkin *et al.* 1999). In addition, they contain bioactives, such as polyphenols, which could have anti-carcinogenic effects, as well as their fermentation products (*i.e.* SCFAs).

Epigenetic mechanisms, such as DNA methylation, may underpin the effects of dietary and other environmental factors on disease risk due to their role in the aetiology of many diseases including cancers such as CRC (Huang *et al.* 2011; Lao & Grady 2011; Schnekenburger & Diederich 2012). Folic acid is found in wholegrains and there is the suggestion that folate status may influence CRC risk (Mathers 2009). However, the evidence linking folate to CRC is complex and studies have reported contradicting results. Therefore, the WCRF/AICR concluded that the evidence for the effects of folate on CRC risk is 'limited–no conclusion' (WCRF/AICR 2018). Due to its role in one-carbon metabolism, folate modulates levels of DNA methylation, consequently gene expression and activity of signalling pathways. Abnormal DNA methylation is observed in CRC, including reduced global DNA methylation levels (hypomethylation) and hypermethylation of tumour suppressor genes, leading to inactivation of these genes (Baylin 2005). In particular, hypermethylation and loss of Wingless/Integrated (WNT) pathway inhibitors have been observed

 

(Galamb *et al.* 2016). The WNT signalling pathway is involved in the regulation of homeostasis and large bowel health via effects on processes such as cell proliferation, differentiation and apoptosis but is aberrantly activated in CRC. *SFRP1*, a WNT antagonists, is hypermethylated in CRC (Caldwell *et al.* 2004) and *SFRP1* methylation has been observed to correlate positively with red blood cell folate concentration (Wallace *et al.* 2010). Associations between plasma and red cell folate have also been observed, whereby these correlated positively with *SFRP1* methylation, as well as additional WNT inhibitors *SFRP2* and *WIF1,* in healthy individuals (Tapp *et al.* 2013). These findings support the notion that folate may induce DNA methylation due to its role as a methyl group donor (Niculescu & Zeisel 2002).

Wholegrains may indirectly influence CRC risk via effects of their bioactive content. For example, some wholegrains are a source of selenium and there is some evidence linking selenium to a reduced risk of CRC (Clark *et al.* 1996; Connelly-Frost *et al.* 2009). However, the WCRF/AICR concluded that this evidence is 'limited–no conclusion' and further studies are required (WCRF/AICR 2018). The proposed underlying mechanisms relate to selenoproteins, which are involved in the maintenance of homeostasis within the large bowel via the regulation of pathways and responses such as the inflammatory response. Meplan and colleagues identified 254 genes and 26 proteins implicated in cancer, immune function, inflammation, cell growth, proliferation, cellular movement and cell death that showed differential expression in the rectal mucosa from healthy participants with higher and lower selenium status (Meplan *et al.* 2016).

Butyrate is a SCFA produced from the fermentation of dietary fibre, in particular those with low fermentability, in the large bowel. The literature suggests that butyrate plays a role in the mediation of lower CRC risk resulting from higher dietary fibre and wholegrain intake, perhaps due to its anti-inflammatory properties (Bultman 2014). In addition, butyrate may modulate CRC risk via its effects on epigenetic mechanisms and is one of the earliest identified epigenetic modifiers (Candido *et al.* 1978). Primarily, butyrate is a histone deacetylase inhibitor (HDACi). HDACis promote gene expression by inhibiting the removal of acetyl groups from histones, which facilitates access by the transcriptional machinery due to a more open chromatin structure (Kurdistani *et al.* 2004). Another epigenetic mechanism modulated by butyrate is the expression of miRNAs. We have shown that in the macroscopically normal colorectum of healthy participants, supplementation with non-digestible carbohydrates (a source of butyrate) for 7 weeks significantly increased the expression of *miR-32*, involved in the regulation of cell proliferation levels (Malcomson *et al.* 2017b). Furthermore, resistant starch significantly reduced the expression of *CTNNB1* and *c-MYC*, as well as *SFRP1,* suggesting further protective effects of dietary fibre via effects on WNT signalling (Malcomson *et al.* 2017a).

### Dairy products

The WCRF/AICR panel concluded that there is probable evidence for a reduction in CRC risk with increased dairy product consumption (WCRF/AICR 2018). The majority of the evidence on dairy products and CRC comes from observational studies and, to date, there have not been any randomised controlled trials. The potential effects of dairy on CRC risk are likely to result from the content of nutrients such as vitamin D and calcium (discussed in the following section), and butyrate. The anti-cancer properties of butyrate, which is also found in the milk of most animals as well as produced in the colon by the microbiome, have been described earlier.

Vitamin D has been associated with effects on many cellular processes implicated in carcinogenesis, including cell proliferation, differentiation and angiogenesis. However, the WCRF/AICR have concluded that the evidence for the relationship between vitamin D and CRC is 'limited–suggestive' (WCRF/AICR 2018). This is because, although the evidence for vitamin D was generally consistent, including in relation to foods containing vitamin D and vitamin D supplements, and dose–response meta-analyses showed significantly decreased CRC risk, the number of studies and quality of evidence are limited. Furthermore, no significant associations have been observed between plasma/serum vitamin D concentrations and CRC risk. The potential effects of vitamin D were first proposed in the 1980s by Garland *et al.* who observed a significant threefold reduced risk of colon cancer in individuals with 25-hydroxyvitamin D (25OHD) concentrations (a marker of vitamin D status) of 20 ng/ml and above (Garland *et al.* 1989). Individuals with 25OHD concentrations between 33 and 41 ng/ml had an 80% lower risk of colon cancer. Vitamin D may have anti-inflammatory effects, which could play an important role in any health-promoting effects in the large bowel. Furthermore, higher vitamin D status has been associated with reducing the risk of IBDs such as ulcerative colitis and Crohn's disease (Ananthakrishnan *et al.*

2012). Approximately a third of IBD patients were reported to be vitamin D-deficient (plasma 25OHD concentrations <20 ng/ml) and, at a median follow-up of 11 years, the deficient patients were at a significantly increased risk of cancers particularly CRC (Ananthakrishnan *et al.* 2014). It has been suggested that the beneficial effects of vitamin D on IBD are likely to be mediated via effects on the immune system (Ardesia *et al.* 2015). The possible chemoprotective properties of vitamin D include its ability to reduce cell proliferation, induce cell differentiation and apoptosis, inhibit angiogenesis and regulate miRNA expression (Fedirko *et al.* 2009; Alvarez-Diaz *et al.* 2012; Padi *et al.* 2013).

Vitamin D has been shown to inhibit WNT signalling, a pathway frequently hyperactive in both sporadic and inherited CRC cases (described in the section on wholegrains and dietary fibre). Several potential mechanisms for the modulation of WNT signalling by vitamin D have been described (Pendas-Franco *et al.* 2008). The active metabolite of vitamin D, 1,25OH2D3, increases the expression of Dickkopf 1 (DKK-1), which is a WNT pathway antagonist. Interestingly, DKK1 has been reported to be hypermethylated and consequently transcriptionally silenced in CRC cell lines (Aguilera *et al.* 2006). Another member of the Dickkopf family, DKK-4, is up-regulated in colorectal tumours and is reduced by 1,25OH2D3 (Matsui *et al.* 2009).

Other dairy product components that may contribute to the effects of dairy on CRC risk include folate, found in cows' milk (5–10 μg per 100 g) and cheese (up to 100 μg per 100 g), growth factors and calcium. The WCRF/AICR panel found consistent evidence for a decreased risk of CRC with higher consumption of dietary calcium, found in dairy products, and concluded that taking calcium supplements 'probably' protects against CRC (WCRF/AICR 2018). The mechanisms underlying the protective effects of calcium include its binding to bile and free fatty acids and effects on cell proliferation and differentiation (described in the following section on calcium supplements). Mammalian milk also contains the growth factors IGF-1 and -II, which, as discussed in the section on body fatness, may affect CRC risk via effects on cell proliferation and apoptosis. Lactoferrin is a glycoprotein found in milk. *In vitro* and animal studies suggest chemoprotective properties of lactoferrin, including inducing apoptosis and reducing inflammation (Ye *et al.* 2014; Jiang & Lonnerdal 2017). In a randomised controlled trial in 104 participants at greater risk of CRC (with adenomatous polyps), supplementation with 3 g/day bovine lactoferrin for 12 months significantly delayed adenomatous polyp growth (Kozu *et al.* 2009). However, this effect was only observed in those aged 63 years or younger. In CRC patients, the clinical outcomes of treatment with lactoferrin supplementation plus chemotherapy did not differ significantly from those observed with chemotherapy only (Moastafa *et al.* 2014).

Dairy products contain fats, particularly triglycerides and fatty acids, as well as fat-soluble vitamins including A, D, E and K, albeit in low amounts in products such as milk. Evidence from *in vitro* studies suggests that the lipids butyric acid and conjugated linoleic acid present in dairy may inhibit proliferation and the induction of differentiation (Jass 1985; Sakata *et al.* 1995; Kien *et al.* 2006). In rats, conjugated linoleic acid is protective against the formation of azoxymethane-induced aberrant crypt foci by approximately 20% (Kohno *et al.* 2002). These effects were associated with a reduction in proliferation and induced apoptosis. Microbes in fermented dairy products may have beneficial effects in the colorectal epithelium that are protective against damage to colorectal cells and consequently CRC development. For example, *Lactobacillus bulgaricus* found in fermented dairy products such as yogurt may protect colorectal epithelial cells by directly binding their apical surface (Sengupta *et al.* 2013). In animal models, *Bifidobacteria* is protective against the development of precursor lesions to CRC, aberrant crypt foci (Challa *et al.* 1997).

### Calcium supplements

Observational and epidemiological studies suggest a protective effect of calcium supplements on the risk of cancers, including CRC, and the WCRF/AICR concluded that the evidence for the effects of calcium supplements at a dose of >200 mg per day on CRC is probable (WCRF/AICR 2018). In a Korean case–control study, comprising 922 CRC cases, significantly reduced CRC risk was observed with the highest calcium intake quartile [odds ratio (OR) 0.16] (Han *et al.* 2015). However, randomised controlled trials have not been able to replicate these findings (Wactawski-Wende *et al.* 2006; Bristow *et al.* 2013). Supplementation of over 26 000 post-menopausal women as part of the *Women's Health Initiative* with 1000 mg/day elemental calcium was not significantly associated with an effect on CRC incidence compared with participants assigned to placebo (Wactawski-Wende *et al.* 2006). In the *Calcium Polyp Prevention*

*Study* group, a randomised controlled trial which supplemented 930 individuals with a recent history of polyps with 3 g calcium carbonate daily or placebo, a 15% reduction in risk of recurrent adenomas (precursors of colorectal cancers) was observed in the calcium group (Baron *et al.* 1999). It has been speculated that calcium may exert a chemoprotective effect by reducing the cytotoxicity of faecal water, decreasing faecal bile acids and secondary bile acid concentrations by binding to these and forming 'calcium soaps' (Lamprecht & Lipkin 2001). Calcium has been proposed to counteract the effects of dietary fat on increasing levels of fatty acids in the large bowel by producing insoluble soaps, thereby counteracting the pro-tumorigenic effects of fat exposure (Newmark *et al.* 1984).

Calcium has also been associated with reducing cell proliferation and promoting differentiation. In the study by Fedirko and colleagues, described in the section on dairy products, expression of p21 (a marker of cell differentiation) increased by 201% in colorectal crypts of participants supplemented with calcium for 6 months compared with placebo (Fedirko *et al.* 2009). The study also analysed effects of the intervention on markers of proliferation and, although there were no significant effects of calcium supplementation on MIB-1 expression, a trend for a 10% reduction in human telomerase reverse transcriptase labelling compared with placebo was reported. However, the evidence on the protective effects of calcium supplementation on colonic crypt cell proliferation has yielded conflicting results (Gregoire *et al.* 1989; Stern *et al.* 1990; Cats *et al.* 1995; Bostick 1997; Cascinu *et al.* 2000). In individuals at increased risk of CRC (first-degree relatives of patients with hereditary non-polyposis CRC), calcium supplementation (in the form of 1.5 g calcium carbonate) three times per day for 12 weeks significantly reduced epithelial cell proliferation by almost 50% compared with baseline (Cats *et al.* 1995). However, these effects did not differ significantly to those observed in the placebo group who received cellulose and starch. In a similar study in patients with familial polyposis, 1.2 g of calcium daily for 9 months significantly reduced rectal cell proliferation levels at 6 months but did not differ significantly to baseline at the end of the study (9 months) (Stern *et al.* 1990). In a trial that supplemented with a greater dose of calcium (2000 mg/day) for 4 weeks, calcium supplementation reduced rectal cell proliferation (Wargovich *et al.* 1992). It may be that the effects of calcium on colonic crypt cell proliferation result from the binding of fatty acids and bile acids (Cats *et al.* 1995).

## Red and processed meats

According to WCRF and AICR, the evidence for the associated increased risk of CRC with intake of processed and red meats is 'convincing' and 'probable', respectively (WCRF/AICR 2018). In the *EPIC* study, involving just under 500 000 participants, a 35% increase in the risk of CRC was observed in participants with a high red and processed meat intake, classified as >160 g per day (Norat *et al.* 2005). However, in the UK, the *National Diet and Nutrition Survey* Rolling Programme for Years 5 and 6 (2012–2014) found that the mean consumption of red (including processed) meat in adults aged 19–64 years was 52 g/day for women and 83 g/day for men (Bates *et al.* 2016).

A meta-analysis of 28 prospective studies concluded that a 14% increase in CRC risk was associated with each 100 g daily increase in total red and processed meat intake (Chan *et al.* 2011). The relative risk (RR) for processed meat was higher than that observed for fresh red meat (RR 1.18 vs. 1.17 per 50 g/day and 100 g/day, respectively). A high red meat intake (characterised by a high saturated fat content) may also modulate CRC cancer risk indirectly via effects on body fatness (discussed earlier) (Vergnaud *et al.* 2010). Linked with this, evidence exists for an increase in the risk of type 2 diabetes with the highest red and processed meat intake by 21% and 41%, respectively, compared with individuals with the lowest intakes (Aune *et al.* 2009). People with type 2 diabetes are at significantly increased risk of developing CRC by approximately 27% compared with those without this condition, proposed to result from effects similar to those related to increased body fatness, such as insulin resistance, inflammation and alterations to the microbiome (Gonzalez *et al.* 2017).

The effects of red meat on CRC risk have been suggested to result from the mutagenic and carcinogenic compounds found in red meat or produced as a consequence of cooking [*e.g.* heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) from cooking at a high temperature] (Cross *et al.* 2003). High concentrations of haem are found in red meat and this has also been associated with processes that may increase CRC risk (Bastide *et al.* 2011). For example, *in vitro* studies have shown that meat haem proteins catalyse lipid peroxidation and oxidation, which produce carcinogenic compounds such as malondialdehyde and also increase oxidative stress (Carlsen *et al.* 2005; Papuc *et al.* 2017). *N*-nitroso compounds, found in processed meats such as bacon

and ham and produced during the curing process (Lijinsky 1999), are mutagens and carcinogens formed by N-nitrosation of haem, amines or amides in the large bowel (Bingham *et al.* 1996; Cross *et al.* 2003; Zhu *et al.* 2014). Another potential mechanisms for the role of red meat in CRC risk include its effect of increasing bile acids (Aykan 2015), which are associated with induced cell proliferation (discussed in the earlier sections on physical activity and calcium supplements).

More recent is the discovery that miRNAs (small, non-coding RNAs that regulate gene expression and consequently affect numerous cellular processes, such as cell proliferation and apoptosis) may play a role in carcinogenesis. Red meat has been shown to modulate the expression of miRNAs, in particular the oncogenic cluster *miR-17-92,* also known as *oncomir-1*, which has been shown to play a role in proliferation, angiogenesis, differentiation and cell survival (Humphreys *et al.* 2014). In a randomised crossover study, a very high red meat diet (300 g/day lean red meat) for 4 weeks significantly increased levels of members of the *oncomir-1* cluster, such as *miR-19a*, *miR-19b* and *miR-21*, by approximately a third in the rectal mucosa of healthy participants. Effects on miRNA expression were associated with an increase in cell proliferation and a reduction in the expression of target genes such as the cell-cycle inhibitor *CDKN1A* and two pro-apoptotic genes *PTEN* and *BCL2L11*. The findings from this study suggest cancer-promoting effects of red meat on expression of the oncogenic *miR-17-92* cluster *in situ* in healthy participants. It must be noted that the dose of red meat given was very high (300 g per day) whereas the WCRF/AICR recommend consuming no more than 500 g per week (equating to 71 g/day, which is similar to the average consumption in the UK).

## Alcohol

Associations between different levels of alcohol consumption and CRC have been reported: chronic alcohol drinking has been associated with increased risk of CRC, among other cancers, particularly those occurring in the gastrointestinal tract. A recent systematic review and meta-analysis of 24 studies investigating the effects of alcohol on CRC incidence reported that alcohol intake, including light drinking (<12.5 g/day alcohol), was associated with an overall 13% increase in CRC risk compared with non/occasional drinking (Wang *et al.* 2015). Even light drinking was associated with a significant increase in CRC risk, albeit by 7%, and heavy drinking (more than 50 g/day alcohol) with a 37% increased risk.

A summary of the promotion of carcinogenesis by alcohol is summarised in Figure 2 (Seitz & Stickel 2007) and will be discussed in the context of CRC within this section. These effects result predominantly from metabolites of alcohol, such as the acetaldehyde, which has carcinogenic properties. Regarding cancer risk, in the healthy cell, alcohol and its metabolites are associated with the generation of ROS and DNA damage (Wu & Cederbaum 2003). It also promotes cell proliferation, affects DNA methylation and impairs the immune function, all mechanisms that have been associated with promoting carcinogenesis. A strong candidate behind these carcinogenic effects is acetaldehyde, a metabolite of ethanol that is a group 1 carcinogen. Concentrations of this carcinogen in the gut are affected by levels of the microbiota or by *Helicobacter pylori* and by enzymes that metabolise ethanol to acetaldehyde (Na & Lee 2017). In turn, alcohol itself may have effects on the microbiome and consequently promote increased levels of acetaldehyde.

Similar to the potential mechanism suggested for carcinogenic properties and effects of red and processed meats described above, alcohol metabolism produces pro-carcinogens such as nitrosamines and polycyclic hydrocarbons via metabolism by CYP2E1 (Poschl & Seitz 2004). Acetaldehyde may cause DNA damage by hindering DNA repair and oxidative capacity, for example by binding and altering enzymes such as O6-methylguanine methyltransferases and glutathione (Seitz & Stickel 2007). DNA damage may also result from DNA adducts formed directly by binding of acetaldehyde and due to an increase in ROS (Seitz & Stickel 2007).

Although other mechanisms induced by alcohol may play a more important role in other cancers, the underlying mechanism for the effects of alcohol on CRC might be its modulation of folate metabolism – for example, oral alcohol ingestion has been shown to acutely reduce serum folate levels in humans (Eichner & Hillman 1973) – and relevant effects on DNA methylation (Boffetta & Hashibe 2006). Alcohol has further effects on DNA methylation indirectly by reducing folate (Halsted *et al.* 2002), consequently leading to aberrant expression of genes implicated in carcinogenesis (Na & Lee 2017). Alcohol may also alter DNA methylation by inhibiting enzymes such as those involved in one-carbon metabolism and DNA methyltransferases, resulting in a reduction in the methyl donor S-adenosylmethionine (Varela-Rey *et al.* 2013). Methylation of genes implicated in CRC,

 

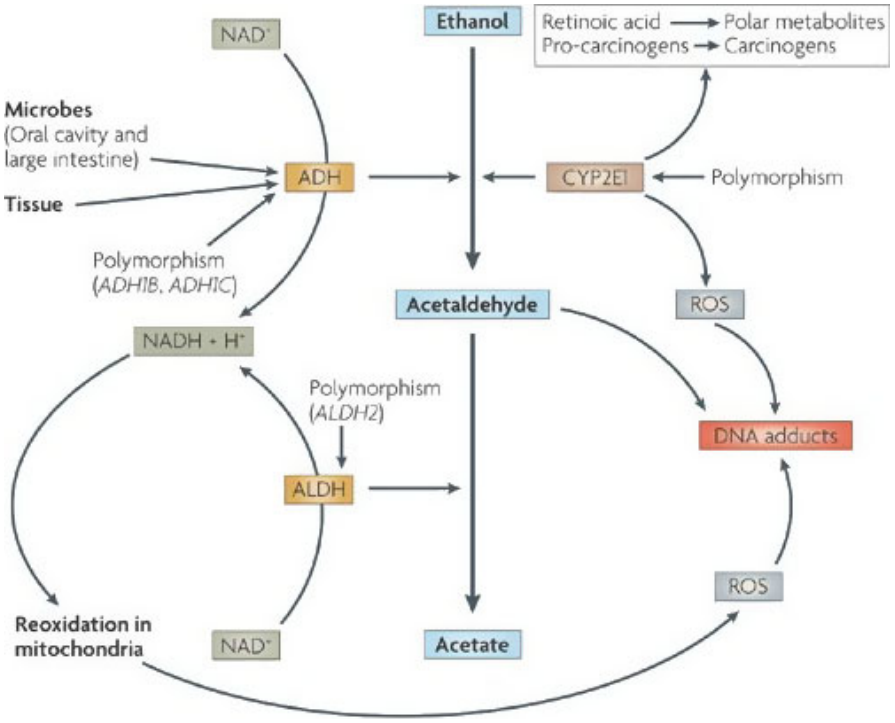


**Figure 2** Alcohol metabolism and mechanisms of alcohol-induced carcinogenesis. Reproduced with permission (Seitz & Stickel 2007). ADH, alcohol dehydrogenase; ALDH, alcohol dehydrogenase; CYP2E1, cytochrome P450 2E1; $NAD^+$, nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide; ROS, reactive oxygen species. [Colour figure can be viewed at wileyonlinelibrary.com]

including the WNT pathway member and tumour suppressor adenomatous polyposis coli (*APC*) and O6-methylguanine-DNA methyltransferases (*MGMT*), a gene frequently hypermethylated in CRC, was investigated in 122 patients with sporadic CRC (van Engeland *et al.* 2003). Individuals with a high alcohol intake (and low folate intake) had increased promoter hypermethylation of these CRC-related genes, compared with those with a low alcohol (and high folate) intake, although the difference was not statistically significant.

## Conclusions

There is substantial and growing evidence of the mechanisms through which individual dietary and lifestyle factors influence cancer pathways and many of these overlap and interact. In the current review, the potential underlying mechanisms for the effects of those concluded by the WCRF/AICR to have strong (convincing or probable) evidence for a relationship with CRC risk were discussed, including physical activity, wholegrains and dietary fibre, red and processed meats and body fatness. A number of mechanisms are common to several of these dietary and lifestyle factors, such as the modulation of inflammation, the microbiome, genomic stability (*e.g.* via effects on DNA damage or repair), insulin resistance and the regulation of processes (*e.g.* cell proliferation and apoptosis) that are vital to the maintenance of large bowel health. More recently, epigenetic mechanisms, such as DNA methylation and microRNA expression, have been implicated in the pathophysiology of cancers including CRC, and evidence exists for modulation of the epigenome by environmental and lifestyle factors such as the intake of dietary fibre and folate.

Better understanding of the mechanisms underlying the protective effects of dietary and lifestyle factors is needed to inform more effective interventions for CRC prevention. Furthermore, stronger evidence, primarily from human studies and ideally randomised controlled trials, is required to confirm the findings from observational studies as well as those performed *in vitro* and in animal models, and to provide evidence for the underlying mechanisms. In the context of the global spread of Western eating patterns and physical inactivity, which promote obesity and, in turn, colorectal carcinogenesis, the need is urgent. However, the complexity of dietary patterns means that studies focusing on individual nutrients provide only a (small) part of

the picture. Future studies that take a more holistic approach, for example by examining dietary and overall lifestyle patterns, may be more appropriate for determining the mechanisms through which lifestyle influences CRC risk and provide a strong foundation for the development of effective interventions to delay or prevent CRC.

## Conflict of interest

The author has no conflict of interests to declare.

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